The Examiner has rejected claims 1, 4-8 and 13-18 under 35 U.S.C. §103(a) asserting that the claims are unpatentable over Contag, et al., (U.S. Patent No. 5,650,135) and Georgiou, et al., (1997 Nature Biotechnology 15:29-34).

The Examiner has objected to claims 9-12 stating that the claims are free of the art of record and would be allowable if rewritten in independent form.

These rejections and objections are believed to be overcome in view of the amendments and arguments discussed below.

Amendment of the Claims

Support for the amendments to claim 1 can be found throughout the specification as originally filed, for example, at the following locations: claims 6-10.

Claims 5 and 11 have been amended to provide correct dependencies for the claims.

Support for newly added claims 25-29 can be found throughout the specification as originally filed, for example, at the following locations: page 8, line 26, to page 9, line 5; and page 23, line 4, to page 25, line 14.

Support for newly added claim 30 can be found throughout the specification as originally filed, for example, at the following locations: page10, lines 5-15; page 14, line13, to page 15, line 10; and page 25, line 15, to page 29, line 8.

Support for newly added claim 31 can be found throughout the specification as originally filed, for example, at the following locations: Figure 3; page 11, lines 11-12; page 16, line 23, to page 17, line 10; and page 36, line 9, to page 37, line 2.

Accordingly, no new matter has been added by way of this amendment and the entry thereof is respectfully requested.

Addressing the Examiner's Rejections

1. Rejections of the Claims Under 35 U.S.C. §103

The Examiner has rejected claims 1, 4-8 and 13-18 under 35 U.S.C. §103(a) asserting that the claims are unpatentable over Contag, et al., (U.S. Patent No. 5,650,135) and Georgiou, et al., (1997 Nature Biotechnology 15:29-34).

The Examiner has addressed the differences between the prior art and the claims at issue (*Graham v. John Deere Co.*, 383 USC 1, 86 S. Ct. 684, 15 L Ed2d 545, 148 USPQ 459, Supreme Court, 1966) as follows:

> Finally, Contag et al disclose the use of antibodies and antibody fragments to confer specificity to the compound. Contag et al. differs from the claimed invention in that they do not specifically disclose the recombinant expression of the antibodies of antibody fragments on the bacterial surfaces. (Office action, dated 2 May 2002, page 4, lines 6-9.)

Applicants submit, however, that there are further, important differences between the cited prior art and the presently claimed invention. Neither Contag, et al., nor Georgiou, et al., teach or suggest the following: a biodetector comprising (1) a signal converting element, comprising (i) an extracellular ligand-specific binding domain which specifically binds a selected substance, wherein said ligand-specific binding domain comprises an epitope-binding fragment of an antibody, and (ii) an intracellular signal transforming domain, (2) a transducer, wherein (i) the transducer has an inactive form and an active form which are distinct from each other, and (ii) the activated intracellular signal transforming domain converts the inactive form of the transducer into the active form of the transducer, (3) a transcription control element, wherein expression mediated by said transcription control element is activated by the active form of the transducer, and (4) a reporter gene operatively linked to said transcription control element.

Specifically there is no teaching in either reference concerning a signal converting element, comprising (i) an extracellular ligand-specific binding domain which specifically binds a selected substance, wherein said ligand-specific binding domain comprises an epitope-binding fragment of an antibody, and (ii) an intracellular signal transforming domain. This is specific situation wherein the signal converting element is a fusion protein wherein the extracellular ligand-specific binding

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domain and the intracellular signal transforming domain are heterologous to one another. Neither reference contains a teaching concerning such a heterologous construct.

According to M.P.E.P. 2143 (Eighth Edition):

To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

In this case, the prior art references do not teach or suggest all of the limitations of the claims of the present invention. Accordingly, applicants believe that the Examiner has failed to establish a *prima facie* case of obviousness.

However, in order to facilitate prosecution, applicants have amended the independent claim (claim 1) to recite the claim limitations of dependent claims 9 and 10. In view of the Examiner's remarks that claims 9-12 would be allowable if rewritten in independent form, applicants submit that the pending claims are now free of the art and in condition for allowance.

Accordingly, in view of the above amendments and arguments, applicants respectfully request that the rejection of the claims under 35 U.S.C. §103(a) be withdrawn.

CONCLUSION

Applicants respectfully submit that the claims comply with the requirements of 35 U.S.C. §112 and define an invention that is patentable over the art. Accordingly, a Notice of Allowance is believed in order and is respectfully requested.

If the Examiner notes any further matters that the Examiner believes may be expedited by a telephone interview, the Examiner is requested to contact the undersigned at (650) 325-7812.

Please direct all further communications in this application to:

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Respectfully submitted,

Date: 3 Sept 2002

By: Gary R Fabian

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APPENDIX A

Marked-up Version of the Claims Showing Amendments Made in this Paper.

1. (Amended) A biodetector for the detection of a selected substance, said biodetector comprising:

a signal converting element, comprising (i) an extracellular ligand-specific binding domain which specifically binds said selected substance, wherein said ligand-specific binding domain comprises an epitope-binding fragment of an antibody, and (ii) an intracellular signal transforming domain derived from PhoQ, wherein binding of said substance to said epitope-binding fragment of said ligand-specific binding domain activates said intracellular signal transforming domain providing an activated intracellular signal transforming domain;

a transducer, wherein (i) said transducer has an inactive form and an active form which are distinct from each other, and (ii) said activated intracellular signal transforming domain converts said inactive form of said transducer into said active form of said transducer;

a transcription control element comprising the phoN promoter, wherein expression mediated by said transcription control element is activated by said active form of said transducer; and

a reporter gene operatively linked to said transcription control element, wherein expression of said reporter gene mediated by said transcription control element causes expression of a reporter gene product that provides a detectable signal, wherein said detectable signal is detected optically by [means selected from the group consisting of] bioluminescence detection [and] or fluorescence detection.

4. The biodetector of Claim 1, wherein said detectable signal is detectable by bioluminescence detection.

5. (Amended) The biodetector of Claim [1] 4, wherein said reporter gene encodes a luciferase.

6. (Cancelled) The biodetector of Claim 1, wherein said signal converting element is a fusion protein where the extracellular ligand-specific binding domain and the intracellular signal transforming domain are heterologous to one another.

7. (Cancelled) The biodetector of Claim 1, wherein said intracellular signal transforming domain is derived from a membrane signal transmitter.

8. (Cancelled) The biodetector of Claim 7, wherein said membrane signal transmitter is from a bacterial two component regulatory system.

9. (Cancelled) The biodetector of Claim 8, wherein said membrane signal transmitter is PhoQ.

10. (Cancelled) The biodetector of Claim 9, wherein said transcription control element comprises the phoN promoter.

11. (Amended) The biodetector of Claim [9] 1, wherein said epitope-binding fragment of an antibody is selected from the group consisting of a single chain variable fragment (ScFv), a Fab fragment, a $F(ab')_2$ fragment, an epitope-binding fragment of a polyclonal antibody, an epitope-binding fragment of a monoclonal antibody, an epitope-binding fragment of a humanized antibody, an epitope-binding fragment of a chimeric antibody, and an epitope-binding fragment of an anti-idiotypic antibody.

12. The biodetector of Claim 11, wherein said epitope-binding fragment of an antibody comprises a single chain variable fragment (ScFv).

13. The biodetector of Claim 1, wherein said biodetector comprises an intact bacterial cell.

14. The biodetector of Claim 13, wherein said biodetector comprises a Gram-positive bacterial cell.

15. The biodetector of Claim 14, wherein said bacterial cell is selected from the group consisting of *Streptococcus, Staphylococcus, Listeria, Clostridium, Bacillus,* and *Corynebacteria.*

16. The biodetector of Claim 13, wherein said biodetector comprises a Gram-negative bacterial cell.

17. The biodetector of Claim 16, wherein said bacterial cell is selected from the group consisting of *Escherichia, Salmonella, Pseudomonas, Helicobacter, Shigella, Proteus, Bordetella, Neisseria, Haemophilus, Bacteriodes, Vibrio, Brucella, Campylobacter, Klebsiella, and Yersinia.*

18. A library of biodetectors, comprising:

at least about 1000 biodetectors of Claim 13, wherein the extracellular ligand-specific binding domain of each of said biodetectors comprises a different antibody fragment.

19. (Cancelled) An expression vector useful for making a fusion protein for use in a biodetector, comprising

(i) a cloning site for insertion of a DNA fragment encoding an extracellular ligand-specific moiety, and (ii) a first DNA fragment encoding an intracellular signal transforming domain,

wherein said vector is capable of expressing a fusion protein comprising (a) a polypeptide encoded by a DNA sequence inserted at said cloning site, and (b) said intracellular signal transforming domain.

20. (Cancelled) The vector of claim 19, wherein the vector further comprises, between said cloning site and said first DNA fragment, a second DNA fragment encoding a membrane anchor.

21. (Cancelled) The vector of claim 19, wherein the vector further comprises, upstream of said cloning site, a third DNA fragment encoding an N-terminal leader sequence.

22. (Cancelled) The vector of claim 19, wherein the vector further comprises, inserted at the cloning site, a fourth DNA fragment encoding an extracellular ligand-specific moiety.

23. (Cancelled) The vector of claim 22, wherein the extracellular ligand-specific moiety comprises an antibody fragment.

24. (Cancelled) The vector of claim 19, wherein the first DNA fragment encodes a polypeptide comprising the cytoplasmic tail of PhoQ.

25. (New) The biodetector of Claim 1, wherein said detectable signal is detectable by fluorescence detection.

26. (New) The biodetector of Claim 25, wherein said reporter gene encodes a fluorescent protein.

27. (New) The biodetector of Claim 5, wherein said luciferase is encoded by a *luc* gene.

28. (New) The biodetector of Claim 5, wherein said luciferase is encoded by a *lux* gene.

29. (New) The biodetector of Claim 13, wherein said bacterial cell comprises a luciferase operon.

30. (New) The biodetector of claim 1, wherein said bioluminescence detection or fluorescence detection is performed using a charge coupled device camera.

31. (New) An ordered array of the library of biodetectors of claim 18.